Reaction of 3,4-Dihydro-β-Carbolines with 4-Fluorophenyl-Nitrile Oxide

Mátyás Milen[a,b], Péter Ábrányi-Balogh[a], András Dancsó[b], Gyula Simig[b] and György Keglevich*[,a]

[a]*Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary*

[b]*EGIS Pharmaceuticals PLC., Division for Chemical Research, H-1475 Budapest, P.O.B. 100, Hungary*

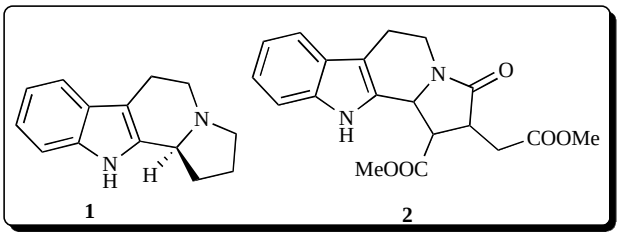
Received February 08, 2010: Revised April 22, 2010: Accepted April 26, 2010

Abstract: The reaction of 3,4-dihydro-β-carboline **5a** with the nitrile oxide generated from 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride (**6**) gave novel adduct **7a** that on standing at 26 °C in $CDCl_3$ was isomerized to species **8**. As an extension, the reaction of the dihydro-β-carbolines substituted on C(1) (**5b-e**) afforded the analogous adducts (**7b-e**). In case of using two equivalents of reagent **6**, the corresponding 1,2,4-triazole-2-oxide (**10b-e**) was also formed beside the adduct (**7b-e**).

Keywords: Alkaloides, 3,4-dihydro-β-carboline, nitrile oxide, cycloaddition, oxadiazolo-pyrido-indole.

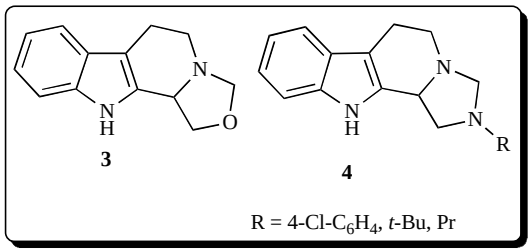
1. INTRODUCTION

The tetrahydro-β-carboline ring system can be found in numerous compounds having interesting biological activities. An optically active form of the tetracyclic alkaloid harmicine (**1**) was isolated from the leaf extracts of Malaysian plant *Kopsia griffithii* [1]. Similar tetracyclic compounds containing the β-carboline skeleton exhibit various biological and pharmaceutical properties. *Meyers* and his coworkers reported on β-carboline compounds (such as **2**) that were used as inhibitors of mitogen-activated protein kinase [2].



1 **2**

Analogues, used in therapy containing two heteroatoms in D ring are also known [3,4].



3 **4**

R = 4-Cl-C_6H_4, *t*-Bu, Pr

We tried to synthesize novel tetracycles containing two or more heteroatoms in D ring.

*Address correspondence to this author at the Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary; Tel: +36 1 4631111/5883; Fax: +36 1 4633648; E-mail: keglevich@mail.bme.hu

2. RESULTS AND DISCUSSION

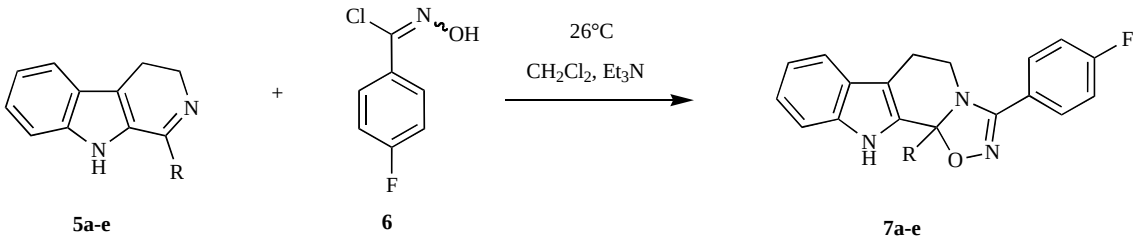
The reaction of 3,4-dihydro-β-carbolines (**5a-e**) with a suitable nitrile oxide seemed to be usable to establish the D ring of the tetracycle. The nitrile oxides are often used in cycloadditions to provide various heterocyclic compounds [5,6]. The corresponding nitrile oxides can be generated *in situ* from the precursors of type chloro-oxime [7] or nitro compound [8].

The starting compounds were 3,4-dihydro-β-carbolines (**5a-e**). In the first approach, the reaction was carried out using 1 equivalent of nitrile oxide generated from 4-fluoro-*N*-hydroxybenzene-carboximidoyl chloride (**6**) in the presence of triethylamine in dichloromethane to give the expected oxadiazolo-pyrido-indole derivatives (**7a-e**) (Scheme **1**) in excellent yields (Table **1**). The structure of the new compounds was confirmed by NMR, IR and mass spectroscopy.

It was found that on standing at 26 °C in an NMR tube, **7a** was converted to isomer **8**. In DMSO-d_6, the extent of isomerization was only several per cent after 4 days, but in $CDCl_3$ after the same period of time, the conversion to **8** was 95%, presumably due to the traces of DCl (Scheme **2**). The NMR spectrum was of diagnostic value, as the sharp singlet of **7a** at 6.80 ppm which was characteristic to the CH unit decreased, while a new, relatively broad peak developed at 8.80 ppm. The latter one is due to the =NH group of the isomerised product **8**. The structure of compound **8** was identified by ^{1}H and ^{13}C NMR data. The assignment was promoted by two-dimensional COSY, HSQC and HMQC spectra.

It is noteworthy that the by-product (**8**) got decomposed slowly in the mixture of acetonitrile–water used as the solvent in the LC-MS analysis. From among the second generation of by-products, tetrahydro-β-carbolinone derivative **9** known from the literature [9] could be isolated, the structure of which was identified by ^{1}H NMR and mass spectroscopy. Beside this, the presence of 4-fluorobenzamide was also pointed out in the mixture by the LC-MS utilizing

1570-1786/10 $55.00+.00



5a-e **6** **7a-e**

R = H(**a**), Me(**b**), Et(**c**), *i*-Pr(**d**), Ph(**e**)

Scheme 1.

an authentic sample. *Corsaro et al*. observed the formal loss of benzonitrile in the case of cycloadducts that were analogous to compound **7a**. The decomposition occurred in several days in solutions at 26 °C in the presence of air [10].

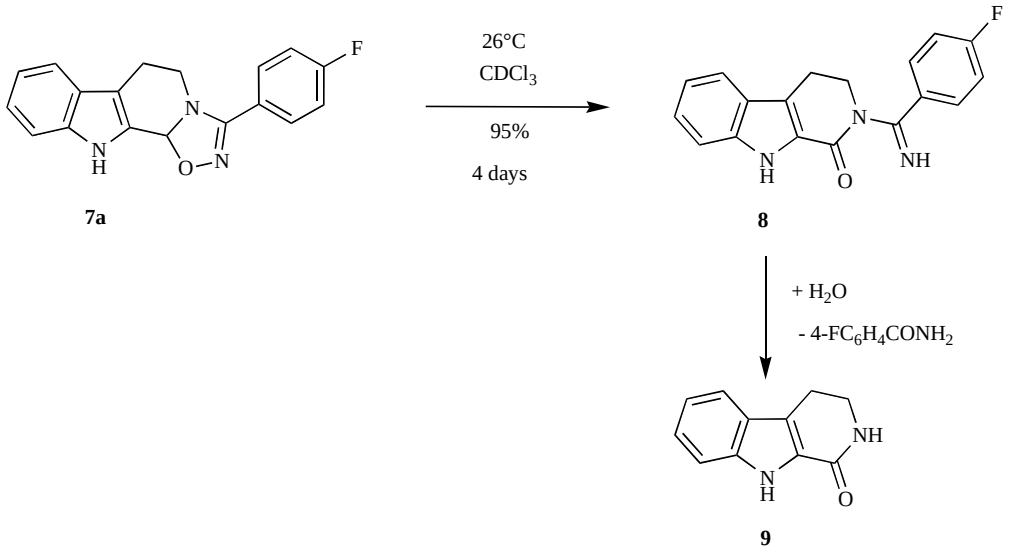
Table 1. Yields of Product Oxadiazolo-Pyrido-Indole Derivatives

Entry	Yield (%)
1	**7a**, 91
2	**7b**, 95
3	**7c**, 98
4	**7d**, 98
5	**7e**, 97

The reaction of 1-methyl-3,4-dihydro-β-carboline (**5b**) was also studied under the same conditions but using 2 equivalents of 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride (**6**). The reaction of **5b** with the corresponding nitrile oxide (generated from **6**) resulted in the formation of two products, tetracycle **7b** and 1,2,4-triazole-2-oxide **10b** (Scheme **3**). The products **7b** and **10b** were obtained in 61 and 35% yield, respectively (Table **2**, entry 2). The structure of the products (**7b** and **10b**) was proved by NMR spectroscopy and single crystal X-ray analysis. Perspective views of **7b** and **10b** are shown in Figs. (**1** and **2**), respectively. We note the folded conformation of **10b** caused by π-π interactions. The 1,2,4-triazole-2-oxide moiety is already known [11], however, to the best of our knowledge, no X-ray structure for it has been reported. Our data confirm the fact that can be expected, according to which the moiety is a typically aromatic one (Fig. **3**).

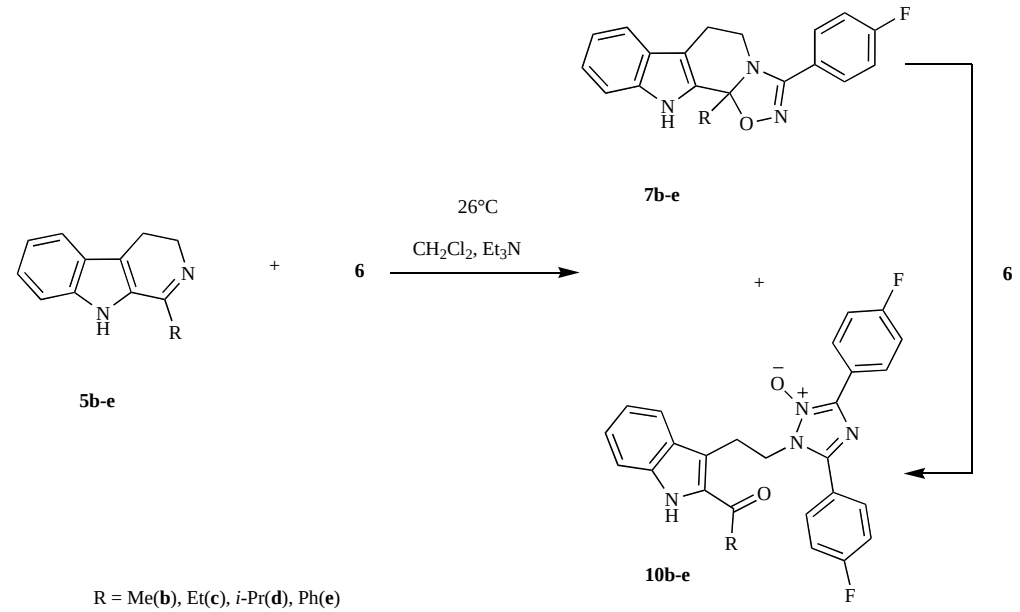
It has been proven that triazole oxide **10b** was formed from cycloadduct **7b** by the addition of a second unit of nitrile oxide. Compound **7b** was reacted with 2 equivalents 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride (**6**) in the presence of triethylamine. In this case, the triazole oxide (**10b**) was isolated in 26% yield. Modelling of the reaction mechanism will be published elsewhere.

After this, the reaction was extended to the 1-ethyl-, 1-isopropyl- and 1-phenyl-3,4-dihydro-β-carbolines (**5c-e**). In all cases, it was found that a mixture of products **7c-e** and **10c-e** was formed (Scheme **3**). Compounds **7c** and **7d** were isolated in *ca*. 60% yield, while **10c** and **10d** were obtained in *ca*. 9% yield (Table **2**, entries 3 and 4). Compounds **7e** and **10e** were prepared in 67 and 33% yields, respectively (Table **2**, entry 5). Products (**7c-e** and **10c-e**) were characterized by NMR and IR spectral data. Compound **7e** was found to crystallize with 0.5 equivalent of acetonitrile. According to thermogravimetric measurement, half of the solvent is lost prior to melting, between 98.6 and 129.8 °C.



7a **8** **9**

Scheme 2.



Scheme 3.

It was not possible to isolate the corresponding triazole oxide from the reaction of **5a** and the nitrile oxide obtained from **6**. However, according to LC-MS, the by-product under discussion was present in the crude mixture in a quantity of 2% (M_r = 444.4).

Table 2. Yields as Indicators of the Product Composition in the Reaction of 3,4-Dihydro-β-Carbolines with a Nitrile Oxide

Entry	Yield (%)	
1	**7a**, 55	
2	**7b**, 61	**10b**, 35
3	**7c**, 61	**10c**, 8
4	**7d**, 60	**10d**, 10
5	**7e**, 67	**10c**, 33

3. EXPERIMENTAL

3.1. General

Melting points were determined on a Kofler-Boëtius micro apparatus and were not corrected. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were taken on a Varian Unity Inova 500 MHz spectrometer. Chemical shifts are downfield to tetramethylsilane. The couplings are given in Hz.

The FT-IR spectra were recorded on a Bruker Vector 22 spectrometer, using KBr pellets of solids. Single crystal X-ray measurements were carried on a Rigaku R-Axis Spider instrument.

3,4-Dihydro-β-carbolines were obtained in a simple procedure from *N*-acyl-tryptamine with phosphorus oxychloride [12,13]. 4-Fluoro-*N*-hydroxybenzenecarboximidoyl

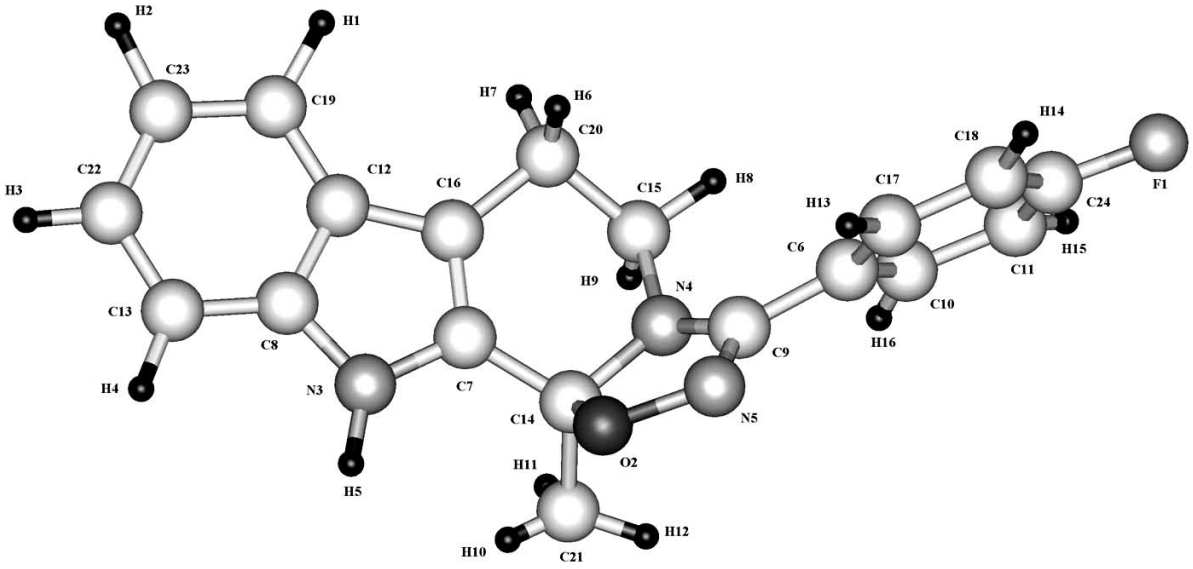


Fig. (1). Perspective view of **7b**.

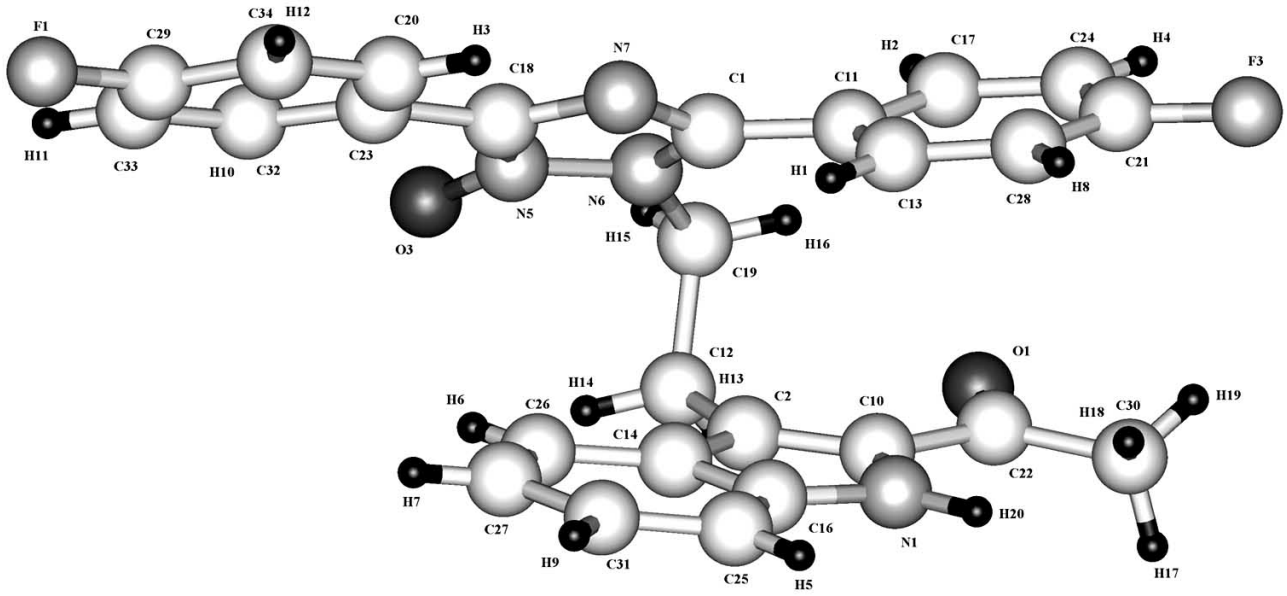


Fig. (2). Perspective view of **10b**.

chloride was synthesized from 4-fluorobenzaldehyde according to the procedure by *Christian Peifer et al.* [14].

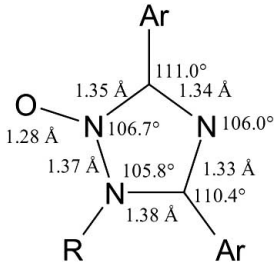


Fig. (3). Selected geometric parameters of the 1,2,4-triazole-2-oxide moiety in **10b**.

3.2. General Method for the Preparation of 7a-e

To a stirred solution of the appropriate 3,4-dihydro-β-carboline derivatives (**5a-e**) (1 mmol) and triethylamine (0.15 ml, 1 mmol) in dichloromethane (20 ml) was added 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride (0.162 g, 1 mmol) in one portion. The solution was stirred at 26 °C until the starting material disappeared (1–8 hours). The reaction mixture was washed with 1% hydrogen chloride (10 ml) and water (2 × 10 ml). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and recrystallised from acetonitrile.

3.3. General Method for the Preparation of 7a-e and 10b-e

To a stirred solution of the appropriate 3,4-dihydro-β-carboline derivatives (**5a-e**) (5 mmol) and triethylamine (1.5 ml, 10 mmol) in dichloromethane (30–80 ml) was added 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride (1.62 g, 10 mmol) in one portion. The solution was stirred at 26 °C for 1 day. The reaction mixture was washed with 5% hydrogen chloride (15 ml) and water (2 × 20 ml). The organic layer was dried ($MgSO_4$) and concentrated to give the product(s). Separation was performed by column chromatography (silica gel, dichloromethane–methanol 99.5:0.5) to give **7a-e** and **10b-e**. Products were recrystallised from acetonitrile.

3.4. 3-(4-Fluorophenyl)-5,6,11,11b-tetrahydro[1,2,4]oxadiazolo[4',5':1,2]pyrido[3,4-*b*]indole 7a

White crystals; mp 170–172 °C; (Found: C, 69.99; H, 4.51; N, 14.02. $C_{18}H_{14}FN_3O$ requires C, 70.35; H, 4.59; N, 13.67%); ν_{max}(KBr)/cm^{-1} 1603, 1507, 1237, 1158, 839 and 744; δ_H($CDCl_3$) 8.41 (bs, 1H), 7.60–7.57 (m, 2H), 7.47–7.45 (m, 1H), 7.37–7.35 (m, 1H), 7.23–7.20 (m, 1H), 7.18–7.14 (m, 2H), 7.12–7.09 (m, 1H), 6.80 (s, 1H), 3.76–3.71 (m, 1H), 3.51–3.49 (m, 1H) and 2.63–2.61 (m, 2H); δ_C($CDCl_3$) 164.2 (d, *J* = 151.0) (CF=), 158.3 (C=), 137.0 (C=), 130.2 (d, *J* = 8.8) (CH=), 129.2 (C=), 126.2 (C=), 123.2 (CH=), 121.3 (d, *J* = 3.4) (C=), 119.9 (CH=), 118.7 (CH=), 116.2 (d, *J* = 22.0) (CH=), 111.7 (CH=), 111.5 (C=), 88.7 (CH), 42.6 (CH_2) and 20.4 (CH_2).

3.5. 2-[(4-Fluorophenyl)(imino)methyl]-2,3,4,9-tetrahydro-1*H*-β-carbolin-1-one 8

δ_H ($CDCl_3$) 9.91 (bs, 1H), 8.80 (b, 1H), 7.62–7.60 (m, 1H), 7.55 (b, 2H), 7.28–7.25 (m, 1H), 7.17–7.14 (m, 1H), 7.09 (~t, *J* = 8.5, 2H), 7.01–6.99 (m, 1H), 4.33 (m, 2H) and 3.22 (t, *J* = 6.5, 2H); δ_C ($CDCl_3$): 163.8 (d, *J* = 250.0) (CF=), 162.1 (CO), 138.3 (C=), 134.2 (C=), 128.4 (CH=), 126.3 (C=), 125.9 (CH=), 124.8 (C=), 122.0 (C=), 120.6 (CH=), 120.5 (CH=), 115.6 (d, *J* = 22.0) (CH=), 112.8 (CH=), 49.4 (CH_2) and 21.3 (CH_2); m/z 307.1132 (M^+ $C_{18}H_{14}FN_3O$ requires 307.1121).

3.6. 3-(4-Fluorophenyl)-11b-1-methyl-5,6,11,11b tetrahydro [1,2,4]oxadiazolo[4',5':1,2]pyrido[3,4-*b*]indole 7b

White crystals; mp 219–221 °C; (Found: C, 70.94; H, 5.04; N, 13.08. $C_{19}H_{16}FN_3O$ requires C, 71.01; H, 5.02; N, 13.08%); ν_{max}(KBr)/cm^{-1} 3201, 1424, 842 and 741; δ_H($CDCl_3$) 8.32 (b, 1H), 7.55 (~dd, J_1 = 5.3, J_2 = 8.8, 2H), 7.44–7.42 (m, 1H), 7.39–7.37 (m, 1H), 7.23–7.20 (m, 1H), 7.15 (~t, *J* = 8.7, 2H), 7.12–7.09 (m, 1H), 3.83–3.78 (m, 1H), 3.46–3.40 (m, 1H), 2.57–2.55 (m, 2H) and 2.03 (s, 3H); δ_C($CDCl_3$) 164.0 (d, *J* = 251.0) (CF=), 158.4 (C=), 136.7

(C=), 132.6 (C=), 130.1 (d, *J* = 8.8) (CH=), 126.3 (C=), 123.0 (CH=), 121.9 (d, J = 3.4) (C=), 119.8 (CH=), 118.6 (CH=), 116.1 (d, *J* = 22.0) (CH=), 111.7 (CH=), 109.9 (C=), 95.9 (C), 42.2 (CH_2), 25.0 (CH_3) and 20.5 (CH_2).

3.7. 1-(3-{2-[3,5-bis(4-Fluorophenyl)-2-oxido-1*H*-1,2,4-triazol-1-yl]ethyl}-1*H*-indol-2-yl)ethanone 10b

White crystals; mp 219–221 °C; (Found: C, 68.02; H, 4.46; N, 12.28. $C_{26}H_{20}F_2N_4O_2$ requires C, 68.12; H, 4.40; N, 12.22%); ν_{max}(KBr)/cm^{-1} 3373, 1657, 1535, 1491 and 1221; δ_H(DMSO-d_6) 11.43 (bs, 1H), 8.46 (~dd, J_1 = 5.5, J_2 = 9.0, 2H), 7.39 (~t, *J* = 8.9, 2H), 7.37–7.35 (m, 1H), 7.22–7.21 (m, 1H), 7.21–7.20 (m, 1H), 7.18–7.14 (m, 4H), 6.78–6.75 (m, 1H), 4.63 (t, *J* = 6.2, 2H), 3.45 (t, *J* = 6.3, 2H) and 2.31 (s, 3H); δ_C(DMSO-d_6) 190.7 (CO), 162.9 (d, *J* = 248.5) (CF=), 162.5 (d, *J* = 247.6) (CF=), 143.0 (C=), 136.0 (C=), 135.8 (C=), 131.9 (C=), 130.1 (CH=), 128.2 (CH=), 127.4 (C=), 125.5 (C=), 123.5 (d, *J* = 2.9) (CH=), 123.2 (d, *J* = 2.9) (CH=), 119.9 (CH=), 119.5 (C=), 116.5 (C=), 115.8 (d, *J* = 22.0) (CH=), 115.5 (d, *J* = 22.0) (CH=), 112.7 (CH=), 44.2 (CH_2), 27.9 (CH_3) and 22.5 (CH_2).

3.8. 11b-Ethyl-3-(4-fluorophenyl)-5,6,11,11b-tetrahydro [1,2,4]oxadiazolo[4',5':1,2]pyrido[3,4-b]indole 7c

White crystals; mp 168–170 °C; (Found: C, 71.31; H, 5.52; N, 12.64. $C_{20}H_{28}FN_3O$ requires C, 71.63; H, 5.41; N, 12.53%); ν_{max}(KBr)/cm^{-1} 3315, 1603, 1512, 1399, 1224 and 1157; δ_H($CDCl_3$) 8.33 (bs, 1H), 7.57 (~dd, J_1 = 5.3, J_2 = 8.6, 2H), 7.44–7.42 (m, 1H), 7.37–7.36 (m, 1H), 7.21–7.19 (m, 1H), 7.16 (~t, *J* = 8.6, 2H), 7.11–7,08 (m, 1H), 3.82–3.78 (m, 1H), 3.44–3.38 (m, 1H), 2.63–2.58 (m, 1H), 2.57–2.54 (m, 1H), 2.39–2.32 (m, 1H), 2.23–2.14 (m, 1H) and 1.17 (t, *J* = 7.3, 3H); δ_C($CDCl_3$) 164.0 (d, *J* = 251.0) (CF=), 158.2 (C=), 136.7 (C=), 132.4 (C=), 130.1 (d, *J* = 8.8) (CH=), 126.3 (C=), 122.9 (CH=), 122.0 (d, *J* = 3.4) (C=), 119.8 (CH=), 118.5 (CH=), 116.1 (d, *J* = 22.0) (CH=), 111.6 (CH=), 110.2 (C=), 98.0 (C), 42.3 (CH_2), 30.4 (CH_2), 20.5 (CH_2) and 7.5 (CH_3).

3.9. 1-(3-{2-[3,5-bis(4-Fluorophenyl)-2-oxido-1H-1,2,4-triazol-1-yl]ethyl}-1H-indol-2-yl)-2-propan-1-one 10c

White crystals; mp 222–224 °C; (Found: C, 68.70; H, 4.72; N, 11.89. $C_{27}H_{22}F_2N_4O_2$ requires C, 68.64; H, 4.69; N, 11.86%); ν_{max}(KBr)/cm^{-1} 3276, 1653, 1491 and 846; δ_H(DMSO-d_6) 11.41 (bs, 1H), 8.44 (~dd, J_1 = 5.6, J_2 = 8.9, 2H), 7.39 (~t, *J* = 8.9, 2H), 7.41–7.34 (m, 1H), 7.21–7.19 (m, 1H), 7.18–7.16 (m, 1H), 7.13–7.11 (m, 4H), 6.75–6.72 (m, 1H), 4.65 (t, *J* = 6.0, 2H), 3.45 (t, *J* = 6.1, 2H), 2.67 (q, *J* = 7.2, 2H) and 0.95 (t, *J* = 7.2, 3H); δ_C(DMSO-d_6) 193.6 (CO), 162.9 (d, *J* = 248.5) (CF=), 162.5 (d, *J* = 247.6) (CF=), 143.1 (C=), 135.9 (C=), 135.8 (C=), 131.5 (C=), 130.1 (d, *J* = 8.8) (CH=), 128.2 (d, *J* = 8.8) (CH=), 127.4 (C=), 125.4 (CH=), 123.5 (d, *J* = 2.9) (C=), 123.2 (d, *J* = 3.4) (C=), 119.8 (CH=), 119.4 (CH=), 116.3 (C=), 115.8 (d, *J* = 22.0) (CH=), 115.47 (d, *J* = 22.0) (CH=), 112.6 (CH=), 44.1 (CH_2), 32.4 (CH_2), 22.5 (CH_2) and 7.6 (CH_3).

3.10. 3-(4-Fluorophenyl)-11b-(1-methylethyl)-5,6,11,11b-tetrahydro[1,2,4]oxadiazolo[4',5':1,2]pyrido[3,4-*b*]indole 7d

White crystals; mp 208–210 °C; (Found: C, 71.93; H, 5.87; N, 12.14. $C_{21}H_{20}FN_3O$ requires C, 72.19; H, 5.87; N, 12.14%); ν_{max}(KBr)/cm^{-1} 3273, 1393, 1223 and 757; δ_H($CDCl_3$) 8.20 (bs, 1H), 7.59 (~dd, J_1 = 5.3, J_2 = 8.8, 2H), 7.46–7.45 (m, 1H), 7.38–7.37 (m, 1H), 7.22–7.19 (m, 1H), 7.16 (~t, *J* = 8.7, 2H), 7.12–7.09 (m, 1H), 3.83–3.79 (m, 1H), 3.51–3.45 (m, 1H), 2.64–2.63 (m, 1H), 2.62–2.60 (m, 1H), 2.54 (~hp, *J* = 6.8, 1H), 1.28 (d, *J* = 6.6, 3H) and 1.04 (d, *J* = 7.0, 3H); δ_C($CDCl_3$) 164.1 (d, *J* = 251.0) (CF=), 158.0 (C=), 136.7 (C=), 131.4 (C=), 130.2 (d, *J* = 8.8) (CH=), 126.4 (C=), 123.0 (CH=), 122.0 (d, *J* = 3.4) (C=), 119.8 (CH=), 118.5 (CH=), 116.1 (d, *J* = 22.0) (CH=), 111.6 (CH=), 111.2 (CH=), 99.9 (C), 43.8 (CH_2), 36.3 (CH), 20.5 (CH_2), 17.5 (CH_3) and 15.9 (CH_3).

3.11. 1-(3-{2-[3,5-bis(4-Fluorophenyl)-2-oxido-1*H*-1,2,4-triazol-1-yl]ethyl}-1*H*-indol-2-yl)-2-methylpropan-1-one 10d

White crystals; mp 188–191 °C; (Found: C, 68.95; H, 4.99; N, 11.48. $C_{28}H_{24}F_2N_4O_2$ requires C, 69.13; H, 4.97; N, 11.52%); ν_{max}(KBr)/cm^{-1} 3351, 1664, 1534, 1489, 1220, 840 and 747; δ_H($CDCl_3$) 8.66 (bs, 1H), 8.55 (~dd, J_1 = 5.5, J_2 = 8.8, 2H), 7.44–7.42 (m, 1H), 7.30–7.29 (m, 1H), 7.29–7.28 (m, 1H), 7.22–7.18 (m, 2H), 7.17(~dd, J_1 = 5.1, J_2 = 8.8, 2H), 6.97–6.94 (m, 3H), 4.75 (t, *J* = 6.5, 2H), 3.65 (t, *J* = 6.5, 2H), 3.05 (hp, *J* = 6.8, 1H) and 1.11 (d, *J* = 6.8, 6H); δ_C($CDCl_3$) 196.7 (CO), 163.6 (d, *J* = 252.0) (CF=), 163.4 (d, *J* = 250.5) (CF=), 143.5 (C=), 137.4 (C=), 135.6 (C=), 130.8 (C=), 129.9 (d, *J* = 8.8) (CH=), 128.6 (d, *J* = 8.3) (CH=), 128.1 (C=), 126.6 (CH=), 123.1 (d, *J* = 3.4) (C=), 123.0 (d, *J* = 2.9) (C=), 121.0 (CH=), 120.3 (CH=), 117.8 (C=), 115.8 (d, *J* = 22.0) (CH=), 115.6 (d, *J* = 21.5) (CH=), 111.8 (CH=), 44.8 (CH_2), 36.9 (CH), 23.6 (CH_2) and 18.8 (2xCH_3).

3.12. 3-(4-Fluorophenyl)-11b-phenyl-5,6,11,11b-tetrahydro[1,2,4]oxadiazolo[4',5':1,2]pyrido[3,4-*b*]indole 7e

White crystals; mp 126–128 °C; (Found: C, 71.98; H, 4.87; N, 12.27. $C_{24}H_{18}FN_3O$ requires C, 74.33; H, 4.86; N, 12.13%); ν_{max}(KBr)/cm^{-1} 3364, 1601, 1454, 1429 and 752; δ_H($CDCl_3$) 8.05 (bs, 1H), 7.61–7.59 (m, 2H), 7.55 (~dd, J_1 = 5.4, J_2 = 8.9, 2H), 7.51–7.49 (m, 1H), 7.42–7.39 (m, 3H), 7.37–7.35 (m, 1H), 7.26–7.24 (m, 1H), 7.16–7.12 (m, 3H), 3.75–3.71 (m, 1H), 3.42–3,36 (m, 1H), 2.69–2.66 (m, 2H); δ_C($CDCl_3$) 164.1 (d, *J* = 251.0) (CF=), 157.4 (C=), 139.9 (C=), 136.9 (C=), 130.5 (C=), 130.13 (d, *J* = 8.3) (CH=), 129.5 (CH=), 128.4 (CH=), 127.6 (CH=), 126.1 (C=), 123.2 (CH=), 121.6 (d, *J* = 2.9) (CH=), 119.9 (CH=), 118.7 (CH=), 116.1 (d, *J* = 22.0) (CH=), 112.3 (C=), 111.7 (CH=), 98.0 (C), 41.2 (CH_2), 20.6 (CH_2).

3.13. (3-{2-[3,5-bis(4-Fluorophenyl)-2-oxido-1*H*-1,2,4-triazol-1-yl]ethyl}-1*H*-indol-2-yl)(phenyl)methanone 10e

White crystals; mp 210–211 °C; (Found: C, 71.39; H, 4.41; N, 10.79. $C_{31}H_{22}F_2N_4O_2$ requires C, 71.53; H, 4.26; N,

10.76%); ν_{max}(KBr)/cm^{-1} 3453, 3131, 1640, 1536 and 1491; δ_H($CDCl_3$) 8.54 (~dd, J_1 = 5.5, J_2 = 7.1, 2H), 8.44 (bs, 1H), 7.60–7.58 (m, 2H), 7.57–7.54 (m, 1H), 7.47–7.44 (m, 2H), 7.31 (m, 1H), 7.30 (m, 1H), 7.26–7.18 (m, 5H), 7.00–6.99 (m, 1H), 6.98–6.95 (m, 2H), 4.72 (t, J = 6.2, 2H) and 3.59 (t, J = 6.2, 2H); δ_C($CDCl_3$) 187.7 (CO), 163.6 (d, J = 251.5) (CF=), 163.3 (d, J = 250.0) (CF=), 143.3 (C=), 138.3 (C=), 137.3 (C=), 135.9 (C=), 132.4 (CH=), 131.2 (C=), 129.9 (d, J = 8.8) (CH=), 128.8 (C=), 128.7 (d, J = 8.3) (CH=), 128.5 (CH=), 128.0 (CH=), 126.8 (CH=), 123.1 (d, J = 2.9) (C=), 123.0 (d, J = 3.4) (C=), 121.3 (C=), 120.6 (CH=), 120.0 (CH=), 115.7 (d, J = 22.0) (CH=), 115.5 (d, J = 22.0) (CH=), 111.8 (CH=), 44.9 (CH_2) and 23.5 (CH_2).

CONCLUSION

In summary, novel fused tetracycles (**7a-e**) were prepared by the reaction of 3,4-dihydro-β-carboline derivatives (**5a-e**) with a nitrile oxide. A novel isomerization of **7a**, and the further degradation of the isomer (**8**) so formed was also observed. Using two equivalents of the nitrile oxide in the reaction of 1-substituted dihydrocarbolines (**5b-e**), the corresponding 1,2,4-triazole-2-oxide (**10b-e**) was also formed. Products **10b-e** were formed from compounds **5b-e** in a second addition reaction.

DEDICATION

Dedicated to Professor József Reiter on the occasion of his 70th birthday.

REFERENCES

[1] Kam, T.-S.; Sim, K.-M. Alkaloids from Kopsia griffithii. *Phytochemistry* **1998**, *47*, 145-147.

[2] Meyers, M.J.; Trujillo, J.I.; Vernier, W.F.; Anderson, D.R.; Reitz, D.B.; Buchler, I.P.; Hegde, S.G.; Mahoney, M.W.; Wu, K.K. Preparation of beta-carboline compounds and analogues thereof for use as mitogen-activated protein kinase-activated protein kinase-2 inhibitors. WO 2005009370, **2005**.

[3] Fourtillan, J.-B.; Fourtillan, M. Preparation of 3H,11H-oxazolo[3',4':1,2]pyrido-[3,4-5b]indole derivatives and therapeutic uses thereof. WO 2007147819, **2007**.

[4] Koletar, G.I.; Frost, J.; Dupont, R.; Lardenois, P.; Morel, C.; Najer, H. Pyrimido and imidazopyridoindolediones and their therapeutic use. EP 18857, **1980**.

[5] Padwa, A. in *1,3-Dipolar Cycloaddition*, Wiley-Interscience: New York, **1984**.

[6] Grundmann, Ch. Synthesis of heterocyclic compounds with the aid of nitrile oxides. *Synthesis* **1970**, *7*, 344-359.

[7] Liu, K.-Ch.; Shelton B.R.; Howe, R.K. A particularly convenient preparation of benzohydroximinoyl chlorides (nitrile oxide precursors). *J. Org. Chem.* **1980**, *45*, 3916-3918.

[8] Mukaiyama, T.; Hoshino, T. The reaction of primary nitro paraffins with isocyanates. *J. Am. Chem. Soc.* **1960**, *82*, 5339-5342.

[9] Bracher, F.; Hildebrand, D. β-Carboline alkaloids. I. Syntheses of 1-aryl- and 1-alkenyl-β-carbolines by palladium-catalyzed coupling reactions. *Liebigs Ann. Chem.* **1992**, *12*, 1315-1319.

[10] Corsaro, A.; Perrini, G.; Caramella, P.; Albini F.M.; Bandiera, T. Selectivity in cycloadditions. XIV. Cycloadducts of benzonitrile oxide to pyridine: a case of a two-step cycloaddition. *Tetrahedron Lett.* **1986**, *27*, 1517-1520.

[11] Gilchrist, T.L.; Harris, C.J.; Hawkins, D.G.; Moody C.J.; Rees, C.W. Synthesis of 1H-1,2,4-triazole 2-oxides and annulated derivatives. *J. Chem. Soc. Perkin Trans. 1. Org. Bioorg. Chem.* **1976**, *20*, 2166-2170.

[12] Kuehne M.E.; Muth, R.S. Total syntheses of yohimbe alkaloids, with stereoselection for the normal, allo, and 3-epiallo series, based on annelations of 4-methoxy-1,2-dihydropyridones. *J. Org. Chem.* **1991**, *56*, 2701-2712.

[13] Hulinska, H.; Taufmann, P.; Frycova H.; Protiva, M. 1-Methyl-, 1-phenyl, and 1-[2-(2-dimethylaminoethoxy)phenyl]-2,3,4,9-tetra-hydro-1H-pyrido[3,4-b]indole and their 2-substituted derivatives. Synthesis and pharmacological screening. *Collect. Czech. Chem. Commun.* **1988**, *53*, 373-380.

[14] Peifer, Ch.; Kinkel, K.; Abadleh, M.; Schollmeyer D.; Laufer, S. From five- to six-membered rings: 3,4-diarylquinolinone as lead for novel p38MAP kinase inhibitors. *J. Med. Chem.* **2007**, *50*, 1213-1221.